Annual Report of the
Howe Laboratory of Ophthalmology, 1945

In common with all organizations that have been concerned with the war effort, the Howe Laboratory began, during the past year, to change its activities to those of peace time. Reconversion of a research laboratory entails not only administrative and financial changes but salvaging and publishing such scientific data resulting from the war researches, as might have general usefulness. Further, it entails a realignment of investigations to accord with the fundamental purposes of a university department in peace time.

Throughout the war the full time staff of the Laboratory has remained intact. Even though the research and development problems undertaken for the Armed Forces and for the Office of Scientific Research and Development resulted in a considerable departure from ophthalmology proper, it was thought that the common good could best be served by having the staff carry on their studies in a laboratory with which they were familiar. Naturally, those of us vitally interested in the advancement of the ophthalmic science regret this departure from basic research on the eye, but such has been the state of civilization for the past several years that the poisonous effects of war gases and the applied optics of range finders have of necessity had prior ratings over pure research.

A brief summary of the investigations carried on during the war can now be given for the first time.

War Gases

The war gas studies, carried on chiefly by Drs. Kinsey and Grant under the direction of the Office of Scientific Research and Development, had as their original purpose the development of an agent that would prevent the toxic effects of mustard gas on the eye. Owing to the considerable latent period between the time of exposure to mustard and the development of the clinical reaction, there was reasonable hope that some agent might be found which, applied during this crucial period, would prevent the deleterious effects from appearing.

In this study especial attention was directed at first to the cornea since this portion of the eye is responsible for the incapacitating effects of mustard. It was early established that mustard penetrated the cornea with great rapidity; its distribution in the cornea could be traced by the use of mustard gas made radioactive. Mustard was found to inhibit the normal turgescibility of the corneal stroma but had no effect on the semipermeability of the corneal epithelium.

A highly sensitive method of measuring mustard in tissue was developed in the Howe Laboratory. By this means it was found that mustard gas applied to the cornea reacted with this tissue and completely disappeared within the first few minutes after contact. Like thermal burns, the initial reaction appeared to be irreversible so that preventive treatment seemed to be the only practical form of therapy.

As an attempt to understand the basic toxic processes by a study directly of the eye proved unsuccessful, the need for biochemical information on the fundamental changes induced by mustard on tissue in general became increasingly apparent. Accordingly, an extensive study was made of the mustard reaction in yeast cells which are more amenable to experimental manipulations. The effects of mustard on yeast growth, carbohydrate metabolism, yeast morphology, and mortality were determined and compared with the effects of other known poisons on yeast. The fate of the mustard within the cells was traced by means of radioactive mustard. Much of the mustard was found to be associated with enzymes and with glutathione. Since enzymes are protein in nature, this finding led to an investigation to determine what portion of a protein molecule (casein) binds with the mustard molecule. The lack of growth of rats whose dietary protein consisted of mustard-treated casein plus selected amino acids was used to indicate what amino acids had been irreversibly bound. The responsible amino acids were found to be methionine and threonine.

Special attention was given to the problem of altering, by oxidation, the mustard in cells after it had once reacted, with the hope that the union of mustard and protein could be reversed. The only means found was too drastic to be applicable for living tissue. Similarly silver, which had been found to split mustard residue from its combination with the amino acid cysteine, was found to be too toxic to the enzyme system studied (urease).

The toxicity of mustard was found to be due in part to its first hydrolytic product, which we have called Semi-H. A method was devised in this Laboratory of synthesizing Semi-H for the first time and thus permitting a study of its toxic properties independent from mustard.

In conclusion it must be stated that the results of these studies extending over the past three years have not succeeded in developing a means of preventing or reversing the reaction of mustard gas on tissues. But what is most discouraging, the facts which have been brought to light showing the rapidity of reactions and the irreversibility of the mustard-protein bond make it unlikely that any therapeutic agent will ever be found for mustard.

The contracts entered into with the Government for the support of the foregoing investigations terminated on December 31, 1945. The results of the investigations are to be published in a series of 14 papers covering the separate phases of the work.

Naval Visual Training Equipment

The development and testing of apparatus used for training in range finding and other gun fire control equipment, has been continuously carried out in the Howe Laboratory since before Pearl Harbor. The work has been under the direction of Dr. Ludvigh and has been carried on through several contracts drawn up between various Navy Bureaus and the Massachusetts Eye and Ear Infirmary.

Attention was first directed to the development of stereoscopic range finding trainers which employed moving objects as targets; the equipment previously employed using stationary targets was found inadequate in training operators to "track" airplanes in flight. Accordingly, an apparatus was designed and built, the Stero-trainer Mark 5, utilizing moving pictures of airplanes in various types of attack. By means of controls similar to those used in actual practice, the trainee then kept the plane on the proper point of the reticule insofar as he was able to discern the position of the plane stereoscopically. The results of each run were automatically recorded and scored, permitting an evaluation of the individual's aptitude for range finding and improvement during training. The results of training with this equipment showed a favorable correlation with those under combat conditions. Based on pilot models constructed in the Laboratory, a standard apparatus using these principles was manufactured in mass elsewhere and has served to train hundreds of stereo range finders throughout most of the war.

In response to a request from the Bureau of Ordnance, an investigation was made in 1942-43 of the stadiometric sights for bomber to fighter fire control. It was found that the sights, then in operation, were not suitable for planes approaching with wing aspect other than horizontal. After considerable experimentation using, again, moving pictures of planes in various types of attack, an annulus type of sight was developed. This proved satisfactory and was adopted by the Navy.

Similarly, other problems which have been worked out in the Laboratory might be described, but space does not permit more than a brief mention of the results. In general, the problems were some of those encountered in changing over from a type of warfare where the targets were relatively stationary to a type where the targets were traveling at high speeds. The Howe Laboratory group carried the assigned problems through the theoretical and experimental stages and then acted in a consultative capacity during the subsequent manufacturing process.

Aside from the studies already mentioned, a few others may be noted briefly. In response to a request from the Bureau of Aeronautics, an exponential return mechanism was developed enabling the conversion of training apparatus using fixed sights to the type using the Draper lead-computing sights. For the Bureau of Ships an especially ingenious device, the so-called CXFV Antenna Simulator, was developed to enable the training of radar operators by the use of simple optical set-ups. In principle this device consisted of substituting light-beam patterns for the radar-emission patterns and a photoelectric cell for the plane. The operating trainee followed the course of the target on a cathode screen just as he would the course of a plane. Other noteworthy contributions were the development of a B. scope plotter and Radar trainer (Mark 9 Spotting) providing training in visual interpretation of radar screens. Both types of apparatus saw service in the Pacific.

The investigations for the Navy are now being gradually terminated. Commander S. Forrest Martin, who had been assigned to the Howe Laboratory for some 56 months, was transferred overseas. Dr. Ludvigh has returned to his former peace-time investigations on a part time basis. It is hoped that by June 1, 1946, the group will have entirely completed its present studies.

Other Studies

An investigation of ultraviolet keratitis which, as noted in previous reports, was begun several years ago, was continued during the past year by Drs. Cogan and Kinsey with the determination of the spectral band responsible for the keratitis. With the data obtained one may make a reasonable inference as to the photosensitive substance in the cornea which gives rise to the reaction. A practical corollary of this investigation was a determination of the relative protection afforded by various types of common glass. Further pertinent studies are currently being made of the transmission of ultraviolet radiation by the ocular media.

Studies on corneal permeability with which the Howe Laboratory has been especially identified during the past several years have been much reduced during the War. However, Dr. Margaret Holt and Dr. Cogan have been able to show the practicability of using electric conductivity (impedance) as an index of ionic permeability for the cornea. The barrier properties of the cornea have been found by this method, as by the chemical method, to depend on the surface membrane, but insofar as rapid changes in permeability may be detected with this method, it provides a valuable adjunct to methods previously employed.

A means has been devised by Drs. Cogan and Kinsey to study regeneration of the endothelium in animal eyes. Experiments are now in progress using this technique to determine some of the nutritional requirements of the endothelium. The aim of these researches is to shed some light on the obscure problem of corneal dystrophies in human beings.

The text on Physiologic Optics by Dr. Ludvigh, which was not quite completed before the War, is now in preparation. A text on the Neurology of the Ocular Muscles by Dr. Cogan is also in the process of completion and is scheduled for publication during the coming year.

With partial reconversion to peace-time research, studies on intraocular fluid dynamics are again in contemplation. Dr. Kinsey has already devised a new method of the micro determination of urea for use in studying the partition of this substance between blood and aqueous humor. Studies have also been started to determine the specificity of ascorbic acid and related compounds in relation to intraocular fluid formation.

Dr. Grant has begun a comprehensive study on toxicology of the eye especially as it relates to industrial substances. Among the potentially hazardous compounds which have been investigated so far are trichlorethylene, propylene oxide, benzoquinone, hydrogen sulphide, butyl acetate, ammonia, sulphur dioxide, and methyl chloride. A further biochemical study is currently being carried out on the toxic properties of methyl alcohol and methyl chloride. These latter have necessitated the development of micromethods for the determination of methyl alcohol, formaldehyde, and formic acid in the blood. Finally, observations have been made on the opticokinetic responses in animals receiving the antiepileptic agent "Triodone". This latter was investigated because of certain visual disturbances occurring in patients receiving this drug.

During the past year Dr. Grant also prepared a timely review article for the Archives of Ophthalmology on the ocular complications of malaria.

Dr. Ludvigh has begun, on a part time basis, a further investigation of those subjects which were interrupted by the War: light difference perception in amblyopia ex anopsia, aimed toward providing a means of differentiating persons with strabismus who may be benefited by orthoptic training from those who will not be benefited; visual acuity based on color perception; visual perception of movement aimed toward a determination of the highest time derivative of space which the human eye can perceive.

Drs. Ludvigh and Kinsey have investigated the effects on vision of exposure to radiant energy in the wave band 320-400 mu in human beings. No deleterious effects were demonstrated using the criteria of light difference perception and critical flicker frequency.

Dr. Albert Lemoine, Jr., was appointed during the past year a Research Fellow in Ophthalmology. This one year appointment made conjointly by the Massachusetts Eye and Ear Infirmary and the Howe Laboratory is intended to further expedite the contacts between research, clinical ophthalmology, and teaching of ophthalmology as well as to afford specialized postgraduate training for the individual.

The entire Howe Laboratory group has continued to make an aggressive effort to cooperate with other research and clinical departments. Dr. Kinsey has continued actively as biochemical consultant for research work being carried out by the Pathology department of the Massachusetts Eye and Ear Infirmary. He has also continued work started a year ago as consultant for the Insect Control Program of the National Academy of Sciences in Washington. Dr. Grant has developed an instrument to be used in conjunction with the Thyroid Service at the Massachusetts General Hospital for the measurement of orbital resiliency. Dr. Cogan has made a clinical study of certain cathode ray burns of the eyes in conjunction with the Radiology department of the Massachusetts General Hospital.

Laboratory Support

The rising cost of services, wages, and materials reduces, in effect, the budget of a department such as the Howe Laboratory which has had a relatively fixed capital. Unless some outside source of income were forthcoming, this could only mean a shrinkage of the Laboratory in comparison with its prewar status. Such a shrinkage would appear most undesirable in view of the increasingly important function which the Laboratory has served since its inception. Accordingly, the hope was expressed at the conclusion of last year's Report that, with the withdrawal of government aid, a means might be found to continue the full activities of the Laboratory. It is, therefore, a great pleasure to acknowledge that at the end of the year, as this report was being prepared, the American Optical Co. graciously offered to give assistance over a period of three years for research in physiologic optics, and the Markle Foundation offered to provide a grant-in-aid for two years in the proposed study of intraocular fluid formation. Only by assistance from such far seeing and generous agencies can the Howe Laboratory hope to maintain and expand its facilities for carrying out basic research in the all-important field of ophthalmology.

David G. Cogan, *Director*

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